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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

6/16/99

MEMORANDUM

SUBJECT: **Tetrachlorvinphos: Revised HED Human Health Risk Assessment**. (Chemical ID No. 083701/List A Reregistration Case No. 0321). DP Barcode No. D256838.

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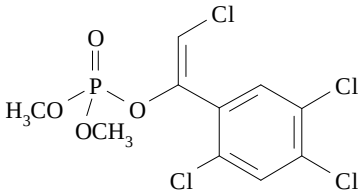
This document serves to revise the 11/2/98 comprehensive human health risk assessment conducted by the Health Effects Division (HED) for the organophosphate (OP) active ingredient **tetrachlorvinphos** [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate] (C. Swartz; 11/2/98). The 11/98 risk assessment served to update the 4/1/98 HED Chapter of the Reregistration Eligibility Document (RED) by incorporating the following: (i) revisions required by the Food Quality Protection Act (FQPA) of 1996; (ii) chronic (non-cancer) and carcinogenic dietary risk assessments using recommended time-limited tolerances and anticipated residues; (iii) carcinogenic risk assessments for occupational and residential exposure; and (iv) risk assessments for acute dietary and short- and intermediate-term residential and occupational exposures for which the Agency had just recently identified toxic endpoints for use in risk assessment.

This revision incorporates: (i) public comments submitted in response to the 11/2/98 risk assessment; (ii) refinement of acute, chronic (noncancer), and carcinogenic dietary risk assessments using anticipated residue data, updated usage figures, and a probabilistic assessment of acute dietary risk; and (iii) review of preliminary findings of a handler exposure study involving placement of tetrachlorvinphos-impregnated collars on pets. Included as attachments are:

Attachment 1. Anticipated residue calculations (C. Olinger; 6/16/99; D256476)
Attachment 2. Revised acute and chronic dietary risk assessment (C. Swartz; 6/16/99;

D256870)
Attachment 3. Revised Occupational exposure and risk assessment (S. Hanley; 6/2/99; D254823 and D256540)



tetrachlorvinphos

In May and June of 1998, meetings were conducted to assess consistency in selecting endpoints and safety factors for all organophosphate pesticides. During these meetings, the HED Hazard Identification Assessment Review Committee (HIARC) selected endpoints for acute dietary and short- and intermediate-term risk assessments for tetrachlorvinphos. The FQPA Safety Factor Committee supported the conclusion that the additional 10X safety factor required under FQPA could be removed (reduced to 1X) for tetrachlorvinphos (refer to the summary documents, "Hazard Assessment of the Organophosphates: Report of the HIARC" and "FQPA Safety Factor Recommendations for the Organophosphates," B. Tarplee and J. Rowland, 7/7/98 and 8/6/98, respectively).

Use patterns supported through reregistration include oral larvicide uses for livestock, direct treatment of beef and dairy cattle (including lactating cattle), horses, poultry and swine; and livestock premise treatments. Homeowner use products allow application to pets and their bedding to control fleas and ticks. Based on these use patterns, dietary exposure through drinking water is not expected to occur. Therefore, residential exposure and dietary exposure through food are the only components of the aggregate exposure and risk assessment for tetrachlorvinphos.

SUMMARY/CONCLUSIONS

Available data indicate that estimated risks associated with chronic (non-cancer) and acute dietary exposures are below the Agency's level of concern. However, carcinogenic risk is above the Agency's level of concern. Chronic and carcinogenic dietary risk estimates were refined using anticipated residue data based on metabolism studies and updated Biological and Economic Analysis Division (BEAD) usage data which estimated the percentage of animals treated via direct dermal treatments and livestock feed-through uses. Acute dietary risk estimates for livestock tissues were based on the recommended time-limited tolerances which were

estimated using metabolism data, and are considered to be worst-case; milk exposure was calculated from USDA's Pesticide Data Program (PDP) monitoring data..

HED is most concerned with risks estimated for handler and post-application residential exposures. The Agency's level of concern is exceeded for both carcinogenic (adults only) and short-term risk associated with contact with treated pets, including dermal contact (adults and toddlers) and hand-to-mouth activity (toddlers). Estimates of carcinogenic risk for tetrachlorvinphos are considered to be very conservative, based on assumptions made regarding the number of applications in a year, the amount/rate applied, and the number of years of pet ownership. No chemical-specific data were used in assessing residential exposures except for preliminary handler exposure data from an unsubmitted study involving placement of impregnated collars on pets. However, the conservative nature of the use assumptions is supported by the results of the National Home and Garden Pesticide Use Survey completed by the Agency in 1992.

A summary of incident reports associated with tetrachlorvinphos usage was presented in the J. Blondell and M. Spann memo dated 7/8/98; relatively few incidents have been reported, and there were no regulatory recommendations made on the basis of these few incidents.

Since residential short-term risks and carcinogenic risks exceed the Agency's level of concern, aggregate risk assessments will not be completed at this time. In the event residential risks are mitigated such that they are beneath the Agency's level of concern, aggregate risks will be calculated. HED reiterates that, based on the supported use patterns, there is no dietary exposure to tetrachlorvinphos expected through consumption of drinking water.

AGENCY RESPONSE TO PUBLIC COMMENTS

The only public comments in response to the 11/2/98 preliminary risk assessment that are directly applicable to the subject revised human health risk assessment were submitted by Hartz Mountain Corp. These are addressed below.

- A series of error comments pertaining to the occupational and residential exposure and risk assessments were incorporated into an earlier version of that assessment by S. Hanley dated 1/7/99 (D251998 and D2522001).

- Hartz Mountain objected to the use of a subchronic (90 day) rat neurotoxicity study as the hazard component of acute dietary and short-term occupational/residential risk assessments; the NOAEL of this study is 4.23 mg/kg/day based upon plasma and red blood cell cholinesterase inhibition at the LOAEL of 43.2 mg/kg/day. Rather, they proposed that the acute rat neurotoxicity study be used for this purpose (NOAEL of 65 mg/kg/day based on transient clinical signs at 325 mg/kg/day that are characteristic of cholinesterase inhibition). HIARC carefully considered both studies during its endpoint

selection. The Committee was aware that neither dosing level nor duration of dosing in either study was optimal for the selection of endpoints for acute and short-term risk assessments. Although cholinesterase inhibition was measured only at the conclusion of the 90-day study, the Committee assumed that the effects could have occurred after a single dose (as demonstrated for other OPs); although clinical signs of neurotoxicity were observed in the acute neurotoxicity study, **the study did not assess cholinesterase inhibition.** Consequently, the cholinesterase inhibition endpoint was selected from the subchronic study

DATA REQUIREMENTS

Residue Chemistry

The residue chemistry data base is considered to be incomplete, largely due to the HED Metabolism Assessment Review Committee (MARC) decision to include 4 tetrachlorvinphos metabolites in the tolerance expression listed under 40 CFR §180.252. In most studies submitted to date, residues of the parent, tetrachlorvinphos were measured. The required residue chemistry data are essential to determine revised tolerance levels in livestock commodities:

OPPTS GLN No. 860.1340: Analytical methods capable of determining tetrachlorvinphos and metabolite residues in meat and milk are required.

OPPTS GLN No. 860.1380: Storage stability data are required for tetrachlorvinphos and its four metabolites in livestock tissues and milk.

OPPTS GLN No. 860.1480: Livestock dermal and feed-through treatment studies are required for poultry, swine and cattle. If all labels are not revised to prohibit treatment of horses intended for slaughter, dermal and feed-through treatment studies on horses are also required.

Occupational and Residential Exposure

Additional data are required to assess dermal and inhalation exposures in indoor residential sites (OPPTS Series 875 Group B Guidelines).

DETAILED CONSIDERATIONS

TOXICOLOGY

Previous versions of HED risk assessments and supporting documents refer to the NOEL (no observed effect level) and LOEL (lowest observed effect level) in toxicology studies. In order to harmonize with other offices in EPA, and to express greater clarity in scientific decision-making, OPP/HED has decided to use the terms no-observed-*adverse*-effect-level (NOAEL) and lowest-observed-*adverse*-effect-level (LOAEL) [policy memorandum, M. Stasikowski, 9/22/98]. The new policy is reflected in the current assessment.

Details of toxicology studies submitted for tetrachlorvinphos are presented in the 4/98 version of the HED RED. Tetrachlorvinphos has relatively low acute toxicity in rats via oral and inhalation routes, and low acute toxicity via the dermal route in rabbits; based on studies conducted in guinea pigs, it is considered to be a dermal sensitizer. In subchronic and chronic toxicity studies conducted in rats and dogs, red blood cell (RBC) and plasma cholinesterase inhibition (ChEI) were observed at doses ranging from 43.2 to 1000 mg/kg/day. Systemic effects observed in these studies included reduced body weights and body weight gains, liver effects including increased liver weights, thyroid effects, and increased kidney weights. Clinical signs of neurotoxicity were not observed in the subchronic and chronic studies.

Developmental and reproductive toxicity studies conducted in rats and rabbits indicate no increased sensitivity of developing young relative to maternal animals due to either pre- or post-natal exposure to tetrachlorvinphos. In acute and subchronic neurotoxicity studies conducted in rats, transient clinical signs characteristic of cholinesterase inhibition were observed, but ChEI was not measured; LOAELs and NOAELs in these studies were either similar to or higher than those in the chronic and subchronic toxicity studies.

In an acute delayed neurotoxicity study conducted in hens, no clinical signs of neurotoxicity or neuropathology were observed; however, inhibition of neurotoxic esterase (NTE) was not assessed. Based on the results of the neurotoxicity studies, and on weight-of-the-evidence consideration of the database, the HIARC concluded a developmental neurotoxicity study is not required for tetrachlorvinphos.

Tetrachlorvinphos is considered to be a possible human (Group C) carcinogen based on statistically significant increases in combined hepatocellular adenoma/carcinomas in mice, and suggestive evidence of thyroid c-cell adenomas and adrenal pheochromocytomas in rats. A cancer potency factor (Q_1^*) of 1.83×10^{-3} $(mg/kg/day)^{-1}$ was estimated using the time-to-tumor model.

Endpoint Selection

Selection of endpoints for tetrachlorvinphos risk assessments was discussed in detail in the 4/98 HED RED Chapter. When endpoint selections for all organophosphates were evaluated for consistency, the HIARC determined that acute dietary and short- and intermediate-term occupational and residential exposure assessments should be conducted for tetrachlorvinphos. A

summary of endpoints for risk assessment is presented in Table 1.

The acute dietary endpoint was selected from an oral subchronic toxicity study conducted in rats, in which plasma and RBC cholinesterase inhibition were observed at the LOAEL of 43.2 mg/kg/day; the NOAEL of 4.32 mg/kg/day is used for acute dietary risk assessment. Although ChEI was measured only at the conclusion of the study (13 weeks), the Committee assumed that the effects could have occurred after a single dose (as demonstrated for other OPs); although clinical signs of neurotoxicity were observed in the acute neurotoxicity study, the study did not assess ChEI. Consequently, the ChEI endpoint was selected from the subchronic study.

The Committee recommended using the endpoint and NOAEL selected from the subchronic toxicity study (ChEI, 4.32 mg/kg/day) for short- and intermediate-term occupational and residential exposure assessments. The Committee had previously selected a dermal absorption factor of 9.57% for dermal exposures, and a 100% absorption factor for inhalation exposures. Although the oral RfD established based on a chronic study in rats was selected for long-term occupational and residential exposure assessments, long-term or chronic exposures are not expected, based on supported use patterns.

Since all the endpoints were selected from animal studies, the conventional safety factors of 10X for intra-species variability and 10X for inter-species extrapolation were applied to determine acceptable margins of exposure (MOEs). The FQPA safety factor was removed (reduced to 1X) for tetrachlorvinphos (see FQPA Safety Factor Recommendations for the Organophosphates, 8/6/98). A reference dose (RfD) which includes the FQPA safety factor (10X, 3X or 1X) is defined as the Population Adjusted Dose (PAD). In the case of tetrachlorvinphos, the acute and chronic PADs (aPAD and cPAD) for the general U.S. population and various population subgroups are equivalent to the acute and chronic RfDs selected by the HIARC. Doses and endpoints for dietary risk assessment are presented in Table 1.

Table 1. Toxicological Endpoints for Risk Assessment.[1]

EXPOSURE SCENARIO	NOAEL (mg/kg/day)	ENDPOINT (LOAEL, mg/kg/day)	STUDY	UNCERTAINTY FACTORS[2]
Acute dietary **aRfD = aPAD = 0.0423 mg/kg/day**	4.23	Plasma/RBC ChE Inhibition at 13 weeks (43.2)	Subchronic Rat	100X (Conventional) 1X (FQPA)
Chronic dietary (non-cancer) **RfD = cPAD = 0.0423 mg/kg/day**	4.23	Histological liver and adrenal changes (43.2)	Chronic Rat	100X (Conventional) 1X (FQPA)
Cancer, $Q_1^* = 1.83 \times 10^{-3}$	NA	Based on adenomas/carcinomas and pheochromocytomas	Mouse carcinogenicity	NA
Short-/Intermediate-Term dermal	4.23	Plasma/RBC ChE Inhibition at 13 weeks (43.2) Use Dermal Absorption Factor of 9.57%	Subchronic Rat	100X (Conventional) 1X (FQPA)
Short-/Intermediate-Term inhalation	4.23	Plasma/RBC ChE Inhibition at 13 weeks (43.2) Use Inhalation Absorption Factor of 100%	Subchronic Rat	100X (Conventional) 1X (FQPA)

[1] NOAEL = No Observed Adverse Effect Level; LOAEL = Lowest Observed Adverse Effect Level; ChE = Cholinesterase; RBC = red blood cell (erythrocyte)

[2] Conventional UF of 100 includes 10X for inter-species extrapolation and 10X for intra-species variability. The FQPA SF was reduced to 1X.

DIETARY EXPOSURE/RISK

HED has recommended revocation of tolerances established in conjunction with application to plants, for which all registrations were voluntarily canceled in 1987. The existing tolerances recommended for revocation are for residues of tetrachlorvinphos *per se* in alfalfa; apples; cherries; field, pop and sweet corn fodder and forage; fresh and sweet corn; corn grain; cranberries; peaches; pears; and tomatoes.

Based on livestock metabolism data, the tolerance expression for tetrachlorvinphos [40 CFR

§180.252] should be amended to include tetrachlorvinphos *per se* and its metabolites des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol. Time-limited tolerances for residues in livestock commodities must be maintained, reflecting feed-through and direct dermal uses on livestock; the recommended time-limited tolerances are based on livestock metabolism data, and exceed existing tolerances for residues in some commodities. Permanent tolerances will be established when adequate magnitude of the residue data for ruminants, swine and poultry are submitted (protocols are under review). **Residues to be included in dietary exposure estimates for incorporation into chronic (noncancer) and carcinogenic risk assessments are tetrachlorvinphos and the four metabolites containing the 2,4,5-trichlorophenyl moiety named above that have been recommended for inclusion in the tolerance expression. Tetrachlorvinphos *per se* is the only residue of acute dietary concern.**

In conducting dietary exposure assessments, HED uses consumption data from USDA's Continuing Surveys of Food Intake by Individuals, 1989-1992. The consumption data are coupled with residues in commodities to determine dietary exposure using DEEM™ Software, purchased under contract from Novigen Sciences, Inc.

For chronic dietary risk assessments, the DEEM™ Software estimates total dietary exposure to pesticides in foods based on mean consumption data. For acute dietary risk assessments, DEEM™ estimates short term (daily) total dietary exposure from individual consumption data. For both acute and chronic dietary exposures, DEEM™ calculates risk by comparing dietary exposure to the endpoints for risk assessment identified by the HIARC.

Refined residue estimates for acute and chronic dietary exposure analysis, generated in conjunction with the HED RED (4/1/98) and used in previous dietary risk analyses, have been updated with the revised usage information. Details regarding calculation of the anticipated residues are provided in the C. Olinger memo (6/16/99; Attachment 1); the refined anticipated residues in livestock commodities are considered to be conservative because of the way in which the data were generated (based on livestock metabolism studies) and because no refinements were made for potential loss of residues during cooking/baking.

In the current chronic (cancer and noncancer) analyses, the weighted average of percent livestock treated was used as a correction factor; for the acute analysis, the estimated (or likely) maximum of percent livestock treated was used. This is a departure from previous HED policy, which dictated use of the estimated maximum percent livestock/crop treated in all analyses. Additional guidance is forthcoming.

Acute and chronic (cancer and non-cancer) dietary exposure analyses conducted for tetrachlorvinphos incorporated DEEM™ default concentration factors. Residue Distribution Files (RDF) were constructed for the probabilistic acute dietary risk assessment using anticipated residues from livestock metabolism studies for tissues and PDP monitoring data for milk. Adjustment for percent livestock treated was made in the RDFs for livestock commodities. For

chronic dietary risk assessments, percent livestock treated adjustments were made in the DEEM™ analysis. In chronic risk assessments, the calculated exposure was compared to the chronic reference dose (cPAD) of 0.04 mg/kg/day and the Q_1* of 1.83 x 10^{-3} $(mg/kg/day)^{-1}$. In the acute risk assessment, the calculated exposure was compared to the acute reference dose (aPAD) of 0.0423 mg/kg/day.

Using the recommended time-limited tolerances, estimated carcinogenic dietary risk for the U.S. Population was 7.94 x 10^{-6} which exceeds the Agency's level of concern (one in a million excess cancers). Refinement of the exposure analysis with anticipated residue data and updated percent livestock treated data resulted in an estimated carcinogenic dietary risk of 1.82 x 10^{-7} for the general U.S. population, which is below the Agency's level of concern for carcinogenic dietary risk.

Refined acute and chronic (noncancer) dietary risk are considerably less than 100% of the acute reference dose (aPAD) and the chronic reference dose (cPAD), respectively, and are therefore considered to be below the Agency's level of concern for acute and chronic (noncancer) dietary risk. These refined risk figures are compared with assessments using time-limited tolerances (as opposed to ARs) and also, for acute risk only, deterministic as opposed to probabilistic approaches. Refer to Table 2 for details. These dietary risk estimates are considered to be conservative, since time-limited tolerances were derived from metabolism data and based on the conservative assumptions made in generating anticipated residues in livestock commodities.

Chronic noncancer dietary exposure and risk estimates indicate the most highly exposed population subgroup is children 1-6 years, with 21% of the cPAD consumed based on use of time-limited tolerances. When refined residue estimates and usage data were incorporated in the analysis, chronic dietary risk was estimated to be <1% cPAD for the general U.S. population and all population subgroups; children 1-6 years were highest, at 0.5% cPAD.

Acute dietary exposure estimated using time-limited tolerances resulted in risks below HED's level of concern. The most highly exposed subgroup was children 1-6 years, with 52% aPAD consumed at the 95th percentile of exposure; the exposure estimate for the general U.S. population corresponded to 29% aPAD consumed. Refinement of the acute dietary exposure estimates using anticipated residues resulted in 46% aPAD for children 1-6 years, and 26% aPAD for the general U.S. population. A probabilistic analysis which incorporated livestock usage data reduced the risk for children 1-6 years to 40% aPAD; the risk for the general U.S. population was reduced to 22% aPAD.

Table 4. Acute and Chronic (Non-Cancer) Dietary Exposure/Risk.

Population Subgroup	Acute **Time-Limited Tolerances** (95th %-ile)		Acute **Anticipated Residues (Deterministic)** (99.5th %-ile)		Acute **Anticipated Residues (Probabilistic**) (99.9th %-ile)		Chronic **Time-Limited Tolerances**		Chronic **Anticipated Residues**	
	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%cPAD	Exposure (mg/kg/day)	%cPAD
U.S. Population	0.012186	29	0.010886	26	0.009345	22	0.004339	10	0.000100	<1
All infants (<1 yr)	0.013767	33	0.011184	26	0.012012	28	0.002664	6.3	0.000060	<1
Nursing infants (<1 yr)	0.008179	19	0.007516	18	0.003347	7.9	0.000983	2.3	0.000013	<1
Non-nursing infants (<1 yr)	0.015706	37	0.012590	30	0.014303	34	0.003371	8.0	0.000080	<1
Children (1-6 yrs)	0.021908	52	0.019692	46	0.017076	40	0.008855	21	0.000193	<1
Children (7-12 yrs)	0.015250	36	0.013633	32	0.010971	26	0.006238	15	0.000140	<1
Females (13-19 yrs)	0.010088	24	0.009548	23	0.008237	19	0.003923	9.3	0.000090	<1
Females (20+ yrs)	0.008426	20	0.007935	19	0.006770	16	0.003217	7.6	0.000080	<1
Males (13-19 yrs)	0.010991	26	0.009821	23	0.008496	20	0.004595	11	0.000095	<1
Males (20+ yrs)	0.009821	23	0.009130	22	0.007606	18	0.003860	9.1	0.000087	<1

OCCUPATIONAL AND RESIDENTIAL EXPOSURE/RISK

Tetrachlorvinphos is marketed in a variety of end-use products that include dusts, emulsifiable concentrates, wettable powders, treated articles, granulars for livestock feed-through purposes, and ready-to-use products (i.e., pressurized sprays and liquids). Tetrachlorvinphos concentrations in various formulations are: dusts (1 to 3 percent), emulsifiable concentrates (2.8 to 24 percent), wettable powders (50 to 75 percent), treated articles (approximately 15 percent), granulars for livestock feed-through purposes (<10 to approximately 98 percent), and ready-to-use products (1 to 2 percent).

Products containing tetrachlorvinphos are intended for use by individuals in the normal course of employment (i.e., they can be occupationally exposed), and can also be purchased and used by homeowners. Some occupational uses can lead to general population exposures in a residential setting (e.g., veterinary or groomer uses on domestic pets). Exposures are typically addressed for those who are involved in the application of pesticides (i.e., handlers or applicators) and those who are exposed to pesticides but who have not directly used them (i.e., post-application exposures). Handlers include professional applicators and homeowners. Post-application exposures include agricultural harvesters or children playing with a treated animal. The Agency anticipates that handler exposures occur in occupational settings, and that both handler and post-application exposure pathways exist for tetrachlorvinphos in residential settings. Handler exposure scenarios are limited to direct animal, premise and feed-through treatments. These scenarios generally indicate that handlers make applications using: ready-to-use packaging, handheld spray equipment, and specialized equipment (e.g., for animal dipping and feed-through applications).

All occupational tetrachlorvinphos exposures were considered to be either short- or intermediate-term in nature; only short-term exposures were considered in residential settings. No chronic exposure scenarios are thought to exist for tetrachlorvinphos. Therefore, short- and intermediate-term exposure/risk assessments were conducted; in addition, a cancer assessment was completed using the Q_1* value estimated by the CPRC and lifetime average daily dose levels (LADDs). **Note that numerical values of short-term and intermediate-term risks are identical because the exposure and hazard components of the risk are the same.**

Occupational Exposures/Risks

Handler Exposure/Risk

Handler assessments were completed for mixer/loaders preparing spray solutions using liquid and wettable powder formulations for applications using handheld equipment and for loading granulars into metering systems for feed-through purposes. Applicator (and combined mixer/loader/applicator) exposures were assessed for commonplace handheld equipment types including backpack, high pressure handwand, and low pressure handwand sprayers. Applicator

exposures were also considered for animal dusting and aerosol can treatments (e.g., livestock and pets).

Occupational handler exposure/risk assessments often indicate a need for risk mitigation in order to ensure that label statements developed as a result of the risk assessment process are adequately protective. Three basic risk mitigation approaches are considered appropriate for controlling occupational exposures. These include administrative controls, the use of personal protective equipment (PPE), and the use of engineering controls. Occupational handler exposure assessments are completed using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an appropriate margin of exposure (MOE) or cancer risk. The baseline clothing/PPE ensemble for occupational exposure scenarios generally consists of an individual wearing long pants, a long-sleeved shirt, no chemical-resistant gloves (except where noted), and no respirator. The first level of mitigation generally applied is PPE; for tetrachlorvinphos, PPE involves the use of an additional layer of clothing, chemical-resistant gloves, and a respirator.

The next level of mitigation considered in the risk assessment process is the use of engineering controls which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include closed tractor cabs, closed mixing/loading/transfer systems, and water-soluble packets. The use of a tiered mitigation approach was used in the completion of the handler exposure/risk assessment for tetrachlorvinphos.

One chemical-specific handler exposure study was submitted in support of the reregistration of tetrachlorvinphos [MRID 42622301, supporting data in MRIDs 44202701 and 44202702]. Separate mixer/loader (16 replicates) and applicator exposures (16 replicates) were quantified during application of a WP formulation in poultry houses using passive dosimetry techniques. Test subjects wore a single layer of clothing and chemical resistant gloves, and applied the formulated product using a high volume/high pressure handwand device. The study was considered to be adequate for regulatory purposes.

Most exposure scenarios were addressed using the data from the *Pesticide Handlers Exposure Database (PHED V1.1)*. PHED was designed by a task force consisting of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a generic database containing voluntarily submitted empirical exposure data for workers involved in the handling or application of pesticides in the field, and currently contains data for over 2000 monitored exposure events. The underlying assumption supporting use of PHED data is that exposure to pesticide handlers can be calculated generically (based on the available empirical data), since exposure is primarily a function of the physical parameters of handling and application process (e.g., packaging type, formulation type, application method, and clothing scenario).

To ensure consistency in the risk assessment process, a surrogate exposure table that contains a series of standard unit exposure values for various occupational exposure scenarios has been

developed using PHED (*PHED Surrogate Exposure Guide of May, 1997*). This guide serves as the basis for the tetrachlorvinphos exposure assessment. The standard exposure values (i.e., the unit exposure values included in the exposure and risk assessment tables) are based on the "best fit" values calculated by PHED. The model calculates "best fit" exposure values by assessing data distributions and then calculates a composite exposure value representing the entire body, ranging from the geometric mean to the median of the selected data set. Exposure values calculated using PHED are of varying quality. Data quality is assessed by considering the analytical (e.g., recovery) and the design qualities of the data (e.g., number of available data points compared to guideline requirements) selected for the assessment. Each value used in the tetrachlorvinphos assessment has a distinct quality associated with it that affects characterization of exposures/risks.

Equipment type and the nature of mixing/loading operations generally define exposure scenarios included in pesticide handler exposure/risk assessments. These scenarios are further refined by application rate ranges and differences in cultural practice (e.g., acres or gallons applied per day vary based on crop). Nine occupational handler scenarios were identified for tetrachlorvinphos; associated exposures and risks were calculated for handlers at all levels of risk mitigation. Mitigation was applied to specific scenarios as required until an acceptable level of risk was attained or until the options for risk mitigation were exhausted.

Exposures for all but one of the nine quantifiable occupational handler scenarios were less than 0.5 mg/kg/day at the baseline clothing scenario. Exposures for most scenarios were less than 0.1 mg/kg/day. The only scenario where exposure exceeded the 0.5 mg/kg/day level was for application using a backpack sprayer. Short- and intermediate-term risks were considered to be below the Agency's level of concern for 6 exposure scenarios at the baseline clothing level using all available data, including the chemical-specific data (i.e., no mixer/loader scenarios, mostly direct animal treatments and other agricultural methods at lower rates).

Since unacceptable risks were estimated for some exposure scenarios at the baseline clothing level, risk mitigation was applied in an attempt to reduce risk. When as assessment was completed for individuals wearing additional clothing layers (e.g., coveralls and gloves) and respirators (as appropriate), exposures were reduced for all scenarios. Only the backpack scenario resulted in an estimated exposure of greater than 0.03 mg/kg/day. **The backpack scenario exposures, even reflecting use of additional PPEs, resulted in MOEs of 4-6, risks well above the Agency's level of concern. Short- and intermediate-term exposures and risk were below the Agency's level of concern for the remaining scenarios after the application of appropriate clothing/PPE risk mitigation measures.** Another risk mitigation option for the Agency is to require the use of engineering controls such as closed tractor cabs and closed mixing/loading systems. These options are not considered to be viable for decreasing risks to tetrachlorvinphos except for the use of water soluble bags for packaging wettable powders (a mitigation which was not needed, since risk was below the Agency's level of concern). There were no data available to calculate exposure and risk associated with the livestock dust application and pellet feed-through scenarios.

Cancer risks were calculated using a Q_1* value of 1.83 x 10^{-3} $(mg/kg/day)^{-1}$ by calculating a lifetime average daily dose (LADD) over a 70 year lifetime. Over this lifetime, individuals were expected to have an average working life of 35 years and to handle tetrachlorvinphos from 3 times per year to one time per week over their working lifetime. **Occupational cancer risks of less than 1 x 10^{-4} were achieved for all scenarios using baseline clothing scenarios (depending on use frequency); however, since risk levels varied based on the number of events per year, risk was unacceptable for some of the higher frequency baseline clothing scenarios. Mitigation through addition of PPE (i.e., additional clothing and gloves) resulted in estimated cancer risks in the 1 x 10^{-5} range at higher use frequencies, and in the 1 x 10^{-6} range or lower for the lower use frequencies**.

Four major input parameters are needed to complete handler risk assessments including unit exposure values specific to the application equipment and level of risk mitigation; application rate; amount that can be treated in a day; and the toxicology parameters. Chemical-specific data discussed above were used to address relevant scenarios, and PHED was used to complete the remaining exposure assessments. Unit exposure values obtained from PHED are assigned a "level of confidence" based on the analytical quality of the selected data and the number of available data points (i.e., high, medium, or low confidence), and generally reflect exposure guideline requirements. For example, in a high confidence data set the analytical qualities of the study meet guideline requirements and include an adequate number of data points. One parameter would be circumspect for medium quality data and both parameters would be circumspect for low confidence data.

In the tetrachlorvinphos handler exposure assessment, data for most scenarios where PHED was used are considered to be low to medium confidence. Maximum application rates were generally used; this is considered to be a conservative assumption, since maximum rates are not commonly used. No chemical-specific use data were available to develop a typical application rate for the cancer component of the risk assessment. Therefore, the maximum application rates for all scenarios were used to complete the cancer assessment. Amortization parameters used to calculate the LADD values (35 working years and up to weekly use over that interval) are likely to over-estimate exposure in the cancer assessment. The estimate of daily treated acres or animals per day is considered to be a reliable estimate of what can be done on a single, very productive day; the daily treated values used in determining tetrachlorvinphos exposures are standard inputs routinely used by the Agency. These estimates are likely to be conservative in estimating cancer risk. A chemical-specific dermal absorption factor (relative to oral dosing) of 9.57 percent was selected by the HIARC and used in the dermal component of all tetrachlorvinphos exposure and risk assessments.

Based on these considerations, the short- and intermediate-term handler exposure and risk assessments are characterized as upper-bound estimates; HED has relatively low confidence in these estimates, due to the quality of the PHED data used. However, for most scenarios, the MOEs that were calculated were considered to be protective, sometimes by large percentages or orders of magnitude. Therefore, the quality of the exposure data may not be as critical in the

evaluation of this assessment. **The cancer assessment should be considered conservative because of the LADD amortization factors and due to the fact that maximum application rates were used for all assessments**.

Post-application Exposure/Risk

Tetrachlorvinphos uses supported through reregistration are not expected to result in significant occupational post-application exposures.

Residential/General Population Exposures and Risk

Handler Exposure/Risk

Handler assessments were completed for individuals applying ready-to-use liquid spray solutions (pressurized aerosols and pump sprays), when dipping or dusting dogs, and when placing a flea collar on an animal.

Handler exposure/risk assessments in the occupational setting often indicate a need for risk mitigation. In the residential setting, however, risk mitigation is not considered to be a viable option in the same manner that it is used in the occupational setting (e.g., extra clothing and a respirator would never be viable on a modern homeowner label because of a lack of training and the ability to enforce such requirements). The only viable risk mitigation options are those inherent in the packaging and formulation such as single use or closed system/coupling products. Unfortunately, exposure data currently used in HEDs assessments do not allow for evaluation of the manner in which subtle product and packaging refinements affect exposure. Therefore, a single clothing scenario was used to calculate exposures for residential handlers (i.e., short pants and short-sleeved shirts, which is thought to be representative of homeowner handlers).

No chemical-specific handler exposure data appropriate for assessing residential handler exposures were submitted in support of reregistration of tetrachlorvinphos. Data from the *Pesticide Handlers Exposure Database (PHED V1.1)* were used as described above for occupational handlers, or approaches detailed in the *Standard Operating Procedures for Residential Exposure Assessment* were used to complete the exposure assessment for residential handlers.

The models described in the *Standard Operating Procedures for Residential Exposure Assessment* were used to calculate residential handler exposures for six residential handler scenarios: dusting or dipping a dog, using an aerosol or a pump sprayer, and for placing a flea collar on a cat or a dog. Some of these scenarios were further divided based upon application rate or source of data (SOPs or preliminary pet collar study) resulting in thirteen residential handler scenario subcategories being identified for tetrachlorvinphos. Estimated exposures (absorbed dose value presented) for all scenarios were less than 0.5 mg/kg/day with a maximum level of 0.46 mg/kg/day calculated for dusting a large animal (i.e., using a whole dust can). The

lowest exposure was 4.4 x 10^{-5} mg/kg/day and most exposure levels were in the 0.1 mg/kg/day range. Short-term residential handler risks were above the Agency's level of concern for 11 of the 13 exposure scenario subcategories; only the use of a pressurized aerosol spray clearly resulted in risks below the Agency's level of concern (MOEs of 2500 or 5300). In the case of pet collar placement, risks derived using the Residential SOPs were somewhat above the Agency's level of concern (MOEs of 86 and 96 for dog and cat, respectively); the registrant's preliminary pet collar placement exposure study indicates MOEs of 280 and 470, respectively. HED will assess this scenario more fully when the final study is submitted.

Residential cancer risks were calculated using a Q_1* value of 1.83 x 10^{-3} $(mg/kg/day)^{-1}$ coupled with a lifetime average daily dose (LADD) over a 70 year lifetime. Over this lifetime, individuals were expected to own pets for either 20 or 40 years of their lives and to treat their pets (or pet living areas) monthly to weekly; use of 2 pet collars per year was assumed). **Residential cancer risks of less than 1 x 10^{-7} were estimated for all collar and pressurized aerosol spray can scenarios. Cancer risks were in the 10^{-7} to 10^{-6} range for all other scenarios (e.g., dusting, dipping, pump sprayer) and risks for these scenarios exceeded 1 x 10^{-6} in some cases. Estimated cancer risks for all but the dust use scenario and the high volume (4 gal) dip scenario subcategory were less than 1 x 10^{-5}; in the dust scenario, use of one can/month for 40 years was assumed**.

Four major input parameters are needed to complete handler risk assessments, including unit exposure values specific to the application equipment and level of risk mitigation; application rate; amount that can be treated in a day; and the toxicology parameters. No chemical-specific exposure data appropriate for use in residential handler assessments were submitted in support of reregistration of tetrachlorvinphos. Several exposure studies (dog dip and dust) are in progress. Preliminary results of an impregnated pet collar placement exposure study were compared to the Residential SOPs (described below). Therefore, either PHED or models described in the SOPs for Residential Exposure Assessment were used to estimate exposure and risk.

The registrant did submit preliminary data on residential handler dermal exposure to pet collars (MRIDs 44780501 and 44780502). The percentage of ai found on the handler's glove from the collar was 0.3 percent. The Residential SOPs assume 1 percent is available. The study is not complete, and this data was set out for comparison only. The total daily absorbed dose calculated from the study data is 0.015 mg/kg/day for dog collars. This results in MOEs >100. The MOEs for the same scenario according to the Residential SOPs is <100 (see Table 13 of Attachment 3). The collar placement exposure study will be reviewed in full when submitted.

The PHED data used were the best available but are still only considered to be medium confidence data due to analytical quality and the number of data points. Maximum application rates were assumed in assessing short-term risk; this approach is considered to be conservative, since maximum application rates are not commonly used. No chemical-specific use data were available to develop a typical application rate for the cancer component of the risk assessment. Therefore, maximum application rates for all scenarios were used to complete the cancer

assessment. The amortization parameters used to calculate the LADD values (20 or 40 years of pet ownership and treatment and up to weekly use over that interval) are considered to be conservative for estimating cancer risk. This characterization is supported by data from the National Home and Garden Pesticide Use Survey completed by the Agency in 1992.

The daily treatment parameters, such as the amount used per day, or the use of an entire can of product, are considered to be reliable upper-bound estimates of daily usage, and are routinely used by the Agency in residential exposure assessments. These assumptions are likely to result in conservative estimates of cancer risk. A chemical-specific dermal absorption factor (relative to oral consumption) of 9.57 percent was selected by the HIARC and used in all assessments.

Based on these considerations, the short-term residential handler assessments for tetrachlorvinphos are characterized as upper-bound estimates of exposure, and are considered to be reliable due to the quality of the PHED data used (aerosol spray scenario only) and the general conservative nature of the SOPs for Residential Exposure Assessment. It should also be noted that for most scenarios, the MOEs were considered to be protective, sometimes by large percentages and even orders of magnitude. Therefore, the quality of the exposure data may not be as critical in the evaluation of this assessment. **The cancer assessment should be considered conservative because of the LADD amortization factors and due to the fact that maximum application rates were used for all assessments**.

Post-application Exposure/Risk

Tetrachlorvinphos is used only for direct animal and animal premise treatment in a residential environment. Note that use of pet collars is considered to result only in handler exposure during placement on the pet. Therefore, postapplication exposure to tetrachlorvinphos resulting from use of pet collars is considered to be negligible. Some significant short-term residential exposure scenarios that have been identified include contact with previously treated pets that translates to considering adult dermal contacts, toddler dermal contacts, and toddler exposures from hand-to-mouth activity following contact with treated pets. In addition, cancer risks were calculated for adults following dermal contact with treated pets.

No chemical-specific data are available to support pet treatments. Therefore, the SOPs for Residential Exposure Assessment were used to address this scenario. In the SOPs, no dissipation is assumed to occur. However, for the purposes of this carcinogenic postapplication risk assessment, a minimal dissipation rate of 14.3% per day was used to approximate dissipation of 1/7 of the applied tetrachlorvinphos per day because the label specifies a minimum 7-day retreatment interval. Then, an average dose representing the interval between applications was used for the cancer LADD calculations.

The dose attributable to short-term dermal contact with treated pets on the day of application for adults ranges from 0.049 to 0.19 mg/kg/day and for toddlers ranges from 0.23 to 0.87 mg/kg/day. The dose for toddlers attributable to hand-to-mouth activity during contact with treated pets

ranges from 4.4 to 8.3 mg/kg/day. In the residential setting, risk mitigation is not considered to be a viable option in the same manner that it is used in the occupational setting (e.g., restricted entry intervals). The only regulatory actions available are the development of more refined data or modification of the use pattern (e.g., alter application rates, remove certain uses, etc.).

Short-term risks were above the Agency's level of concern for all adult exposure scenarios; MOEs were 23-86. All toddler MOEs were less than 18 (acceptable = 100) for the dermal scenario and less than 1 when hand-to-mouth activity was considered. Time weighted average values were used to calculate adult cancer risks resulting from dermal contact with a treated animal. These residential cancer risks were calculated using a Q_1* value of 1.83×10^{-3} $(mg/kg/day)^{-1}$ by calculating a lifetime average daily dose (LADD) over a 70 year lifetime. Over this lifetime, individuals were expected to own pets for either 20 or 40 years of their lives and to treat their pets (or pet living areas) 5 to 12 times per year. **Residential postapplication carcinogenic risks were 3.4×10^{-6} to 3×10^{-5}. Residential carcinogenic risks were also aggregated because it is likely that multiple types of treatment will occur in the residential setting in the same year and that the same individual will serve as the handler as well as be exposed postapplication. Aggregated residential handler plus postapplication carcinogenic risks reflecting 5 or 12 applications of a single treatment type (i.e., dip, aerosol, powder, or pump spray) were calculated to be 4×10^{-6} to 3.1×10^{-5}. Combining two treatment types resulted in carcinogenic risks of 4.3×10^{-6} to 3.9×10^{-5}; the handler and postapplication components each contributed about 50% each to the total carcinogenic risk.**

The short-term post-application dose levels calculated for adults and toddlers based on dermal contact and on hand-to-mouth activity for toddlers are considered to be conservative because the dose levels calculated for a single exposure pathway are generally orders of magnitude greater than those indicated by available population-based biological monitoring data. Maximum application rates were assumed, and little or no dissipation was considered. Furthermore, the models use overly conservative estimates for residue transfer and ingestion (e.g., 100 percent of material on the hand is transferred) in each hand-to-mouth event.

Maximum application rates for all scenarios were also used in assessing cancer risk, and the amortization parameters used to calculate the LADD values (20 or 40 years of pet ownership and treatment and up to weekly use over that interval) were conservative in nature. This characterization is supported by data from the National Home and Garden Pesticide Use Survey completed by the Agency in 1992.